NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 408

TOXICOLOGY AND CARCINOGENESIS STUDIES OF MERCURIC CHLORIDE

(CAS NO. 7487-94-7)

IN F344 RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

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P.O. Box 12233
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CONTENTS

ABSTRACT

$HgCl_2$

MERCURIC CHLORIDE

CAS No. 7487-94-7

Chemical Formula: $HgCl_2$ Molecular Weight: 271.5

Synonyms: Abavit B, calochlor, corrosive sublimate, dichloromercury, mercuric bichloride, mercury chloride, mercury (II) chloride, mercury bichloride, mercury perchloride, sublimate, sulem, bichloride of mercury, corrosive mercury chloride, perchloride of mercury, mercury dichloride

Trade name: Fungchex

Mercuric chloride is an inorganic compound that has been used in agriculture as a fungicide, in medicine as a topical antiseptic and disinfectant, and in chemistry as an intermediate in the production of other mercury compounds. The widespread use of mercury has resulted in increased levels of mercury in rivers and lakes. Mercuric chloride was evaluated in toxicity and carcinogenicity studies because of its extensive use and its occurrence as an environmental pollutant, and because of the lack of adequate long-term rodent studies.

Toxicology and carcinogenesis studies were conducted by administering mercuric chloride (greater than 99% pure) in deionized water by gavage to groups of F344 rats or $B6C3F_1$ mice for 16 days, 6 months, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* (strains TA98, TA100, TA1535, and TA1537), in mouse lymphoma L5178Y cells, in Chinese hamster ovary cells, and in *Drosophila melanogaster.*

16-Day Studies

Groups of five rats of each sex received 0, 1.25, 2.5, 5, 10, or 20 mg mercuric chloride/kg body weight and groups of five mice of each sex received 0, 5, 10, 20, 40, or 80 mg/kg in deionized water by gavage for 12 dose days. Two male rats in the 20 mg/kg group died in the first week, as did all male and four female mice from the 80 mg/kg group and one male mouse from the 40 mg/kg group. The final mean body weight of male rats receiving 20 mg/kg was 10% lower than that of the controls; the final mean body weight of 20 mg/kg females was 9% lower than that of the controls. Final mean body weights and body weight gains of dosed mice were similar to those of the controls. Absolute and relative kidney weights of male rats receiving 2.5 mg/kg or greater doses and of female rats administered 5 mg/kg or more were significantly greater than those of the controls. Absolute kidney weights of mice were significantly increased in all male dose groups and in the 40 mg/kg female dose group; relative kidney weights of dosed male and female mice were significantly greater than the controls. Analysis of kidney, liver, and brain tissues for mercury residues revealed that the highest mercury concentration was in the kidneys of rats and mice. Acute renal tubule nephropathy occurred in dosed rats and was slightly more severe in males than in females. Chemical-related lesions in mice included renal tubule necrosis, inflammation and necrosis of

the forestomach, and necrosis of the glandular stomach.

6-MONTH STUDIES

Groups of 10 rats of each sex received 0, 0.312, 0.625, 1.25, 2.5, or 5 mg mercuric chloride/kg body weight in deionized water by gavage for 26 weeks. Groups of 10 mice of each sex received 0, 1.25, 2.5, 5, 10, or 20 mg/kg in deionized water by gavage for 26 weeks (males) or 27 weeks (females). No deaths related to mercuric chloride administration occurred in rats or mice. Mean body weight gains of male rats that received 5 mg/kg and all female rat dose groups that received 0.625 mg/kg or greater were significantly lower than the controls. The final mean body weight and body weight gain of male mice in the 20 mg/kg group were significantly lower than those of the controls; final mean body weights and body weight gains of other dosed male mice and all dosed female mice were similar to those of the controls. Absolute and relative kidney weights of all dosed male rats and of female rats that received 0.625 mg/kg or greater were significantly greater than those of the controls. In male mice, absolute kidney weights in the three highest dose groups were significantly increased; no biologically significant differences in organ weights occurred in female mice. Analysis of kidney, liver, and brain tissues for mercury residues revealed the highest mercury concentration in the kidneys of rats and mice. The severity of chronic nephropathy increased with dose in male rats. Cytoplasmic vacuolation of renal tubule epithelial cells was observed in male mice in the 5, 10, and 20 mg/kg groups. No histopathologic changes in female mice were related to chemical exposure.

2-YEAR STUDIES

Groups of 60 rats of each sex received 0, 2.5, or 5 mg mercuric chloride/kg body weight and groups of 60 mice of each sex received 0, 5, or 10 mg/kg in deionized water by gavage 5 days per week for 2 years. The doses were based on decreased weight gains in rats receiving 10 and 20 mg/kg and the decreased weight in male mice receiving 40 mg/kg during the 16-day studies, and on the decreased weight gains and toxicity results seen in the 6-month studies. Increased absolute and relative kidney weights in rats and male mice in the 6-month studies and degenerative renal changes suggested that higher dose levels would result in inadequate survival rates for a 2-year study.

15-Month Interim Evaluations

Relative kidney weights were significantly increased in dosed rats and female mice. The severity of nephropathy was increased in male rats, but not in females. High-dose male and female rats had minimal to mild hyperplasia of the basal cell layer in the forestomach epithelium (diagnosed as acanthosis); this lesion was not found in control or low-dose rats. Male mice had an increased severity of vacuolation of the renal tubule epithelium; no chemical-related lesions occurred in the kidneys of females. The incidence of inflammation of the olfactory epithelium lining the nasal cavity increased in male and female high-dose mice.

Survival, Body Weights, and Clinical Signs

Survival of dosed male rats was lower than that of the controls (26/50, 10/50, 5/50); survival of dosed female rats was similar to that of the controls (35/50, 28/49, 30/50). Although more than 60% of the mice in each dose group survived to study end, survival rates of high-dose male mice and dosed female mice were lower than those of the controls (males: 36/50, 36/50, 31/50; females: 41/50, 35/50, 31/50). The final mean body weights of high-dose male and female rats were 15% and 14% lower than controls, respectively. The mean body weight of low-dose female rats was generally similar to controls throughout the 2-year study; the mean body weight of low-dose male rats was similar to that of the control through week 89. In mice, mean body weights of all male and female dose groups were similar to those of the controls throughout the studies.

Pathology Findings

Chronic nephropathy appeared to develop at an accelerated rate and led to decreased survival in both dosed male rat groups. Secondary effects of renal dysfunction in dosed male rats resulted in increased incidences of fibrous osteodystrophy of the bone, mineralization of various tissues, and parathyroid gland hyperplasia. Based on evaluations of single and step sections, the incidence of renal tubule hyperplasia was increased in high-dose male rats (control, 3/50; high-dose, 10/50), but the incidences of renal tubule adenoma in high-dose and control males were similar (4/50, 5/50). Renal tubule hyperplasia was also slightly increased in high-dose female rats (2/50,

5/50) and adenomas were seen in high-dose females, but not in controls (0/50, 2/50).

Incidences of forestomach hyperplasia in rats were markedly increased in dosed males (3/49, 16/50, 35/50) and high-dose females (5/50, 5/49, 20/50). Squamous cell papillomas of the forestomach were found in 3 low-dose and 12 high-dose males and in 2 high-dose females. No squamous cell carcinomas were found.

The incidence of thyroid follicular cell carcinoma was marginally increased in high-dose male rats (1/50, 2/50, 6/50). However, a corresponding increased incidence in follicular cell adenomas (1/50, 4/50, 0/50) or hyperplasias (2/50, 4/50, 2/50) in males did not occur, and the overall incidence of follicular cell neoplasms was not significantly increased (2/50, 6/50, 6/50).

The incidence of nasal mucosa inflammation in male and female rats was increased in the high-dose groups (male: 9/50, 8/47, 18/50; female: 0/49, 5/49, 15/50) and may have been related to chemical administration. The incidences of mammary gland fibroadenomas were significantly decreased in dosed female rats (15/50, 5/48, 2/50).

The incidence and severity of nephropathy were increased in dosed mice; secondary effects of renal dysfunction did not occur. Renal tubule hyperplasia was found in one control and two high-dose male mice. Two renal tubule adenomas and one renal tubule adenocarcinoma were seen in high-dose male mice. Additional step sections revealed focal hyperplasia in another control male; no additional renal tubule neoplasms were found in high-dose or control males. Proliferative lesions of the renal tubule epithelium were not found in female mice.

The incidence of metaplasia of the olfactory epithelium increased with dose in male and female mice. No other biologically significant lesions were found.

GENETIC TOXICOLOGY

Mercuric chloride was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 with or without exogenous metabolic activation (S9). Induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* did not occur when mercuric chloride was administered in feed or by injection. However, positive results were obtained in mutagenicity tests with mammalian cells. In the absence of S9, mercuric chloride induced trifluorothymidine resistance in mouse L5178Y cells and chromosomal aberrations in Chinese hamster ovary cells. In the Chinese hamster ovary cell test for induction of sister chromatid exchanges, mercuric chloride produced a negative response without S9 and a weakly positive response in the presence of S9.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of mercuric chloride in male F344 rats based on the increased incidence of squamous cell papillomas of the forestomach. Marginally increased incidences of thyroid follicular cell adenomas and carcinomas may have been related to mercuric chloride exposure. There was *equivocal evidence of carcinogenic activity* of mercuric chloride in female F344 rats based on two squamous cell papillomas of the forestomach. There was *equivocal evidence of carcinogenic activity* of mercuric chloride in male $B6C3F_1$ mice based on the occurrences of two renal tubule adenomas and one renal tubule adenocarcinoma. There was *no evidence of carcinogenic activity* of mercuric chloride in female $B6C3F_1$ mice receiving 5 or 10 mg/kg.

Nonneoplastic lesions associated with exposure to mercuric chloride included increased severity of nephropathy in male rats and male and female mice. There was an increased incidence of renal tubule hyperplasia in male rats. The incidence of forestomach hyperplasia was increased in dosed male and female rats. Increased incidences of nasal mucosa inflammation were associated with mercuric chloride administration in rats. Increased incidences of olfactory epithelial metaplasia in mice were also associated with mercuric chloride administration.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the peer review comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenicity and Genetic Toxicology Studies of Mercuric Chloride

Male F344 Rats	Female F344 Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 2.5, or 5.0 mg/kg in deionized water by gavage at a dose volume of 5 mL/kg	Same as male rats	0, 5, or 10 mg/kg in deionized water by gavage at a dose volume of 10 mL/kg	Same as male mice
Final body weights			
Dosed groups less than vehicle controls	Dosed groups less than vehicle controls	Dosed groups similar to vehicle controls	Dosed groups similar to vehicle controls
2-year survival rates			
26/50, 10/50, 5/50	35/50, 28/49, 30/50	36/50, 36/50, 31/50	41/50, 35/50, 31/50
Nonneoplastic effects			
Kidney: nephropathy (50/50, 46/50, 48/50); nephropathy average severity grades (2.66, 3.14, 3.32); renal tubule hyperplasia (3/50, 0/50, 10/50)	Forestomach: papillary hyperplasia (5/50, 5/49, 20/50)	Kidney: nephropathy (40/50, 45/50, 44/49); nephropathy average severity grades (1.08, 1.74, 2.51);	Kidney: nephropathy (21/49, 43/50, 42/50); nephropathy average severity grades (0.47, 1.02, 1.24)
Forestomach: papillary hyperplasia (3/49, 16/50, 35/50)	Nasal mucosa: inflammation (0/49, 5/49, 15/50)	Nasal mucosa: olfactory epithelial metaplasia (3/50, 8/50, 41/50)	Nasal mucosa: olfactory epithelial metaplasia (1/50, 20/50, 46/50)
Nasal mucosa: inflammation (9/50, 8/47, 18/50)			
Neoplastic effects			
Forestomach: squamous cell papilloma (0/50, 3/50, 12/50)	None	None	None
Uncertain findings			
Thyroid: follicular cell adenoma (1/50, 4/50, 0/50); follicular cell carcinoma (1/50, 2/50, 6/50)	Forestomach: squamous cell papilloma (0/50, 0/49, 2/50)	Kidney: renal tubule adenoma (0/50, 0/50, 2/49); renal tubule adenocarcinoma (0/50, 0/50, 1/49)	None
Levels of carcinogenic activity			
Some evidence	Equivocal evidence	Equivocal evidence	No evidence
Genetic toxicology			
Salmonella typhimurium gene mutation:	Negative with and without S9 in strains TA100, TA1535, TA1537, and TA98		
L5178Y mouse lymphoma cell gene mutation:	Positive for induction of trifluorothymidine resistance without S9		
Sister chromatid exchange Chinese hamster ovary cells *in vitro*:	Weakly positive with S9; negative without S9		
Chromosomal aberration Chinese hamster ovary cells *in vitro*:	Positive without S9; negative with S9		
Sex-linked recessive lethal mutations *Drosophila melanogaster* germ cell mutation:	Negative administered by injection or in feed		

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results **clear evidence** and **some evidence**; one category for uncertain findings **equivocal evidence**; one category for no observable effects **no evidence**; and one category for experiments that because of major flaws cannot be evaluated **inadequate study**. These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.

- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.

- **Inadequate study** of carcinogenic activity describes studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on mercuric chloride on July 10, 1991, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE

On July 10, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of mercuric chloride received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. G.A. Boorman, NIEHS, introduced the toxicology and carcinogenesis studies of mercuric chloride by discussing the uses and rationale for study. describing the experimental design including analysis of tissue and organ levels of mercury during a 6-month study, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in rats and mice. In summary, he thought the main concern with mercuric chloride should be toxicity, more so than carcinogenicity. The proposed conclusions were *some evidence of carcinogenic activity* in male F344 rats, *equivocal evidence of carcinogenic activity* in female F344 rats and male B6C3F$_1$ mice, and *no evidence of carcinogenic activity* in female B6C3F$_1$ mice.

Mr. Beliczky, a principal reviewer, agreed in principle with the conclusions. He thought that a statement regarding thyroid neoplasms in male rats should be deleted. He expressed concern that carcinogenicity data generated from the studies appeared to be compromised by the chemical toxicity, particularly in the kidney. Mr. Beliczky stated that if the severe toxicity of the chemical clearly limited the sensitivity of the study to detect carcinogenic effects, then the study design was limited or should have been modified after the 6-month study. Dr. Boorman agreed that in some cases, toxicity may have interfered with the ability to assess carcinogenicity.

Dr. Garman, the second principal reviewer, agreed with the conclusions. In view of the importance of the renal toxicity and the continuum which exists between hyperplasia, adenoma, and carcinoma, he suggested inclusion of a photomicrograph of a representative lesion of renal tubule hyperplasia (Plates 3 and 4).

Dr. Goodman, the third principal reviewer, agreed with the conclusions with the exception that he thought the second sentence should be qualified to read: "A marginally increased incidence of thyroid follicular cell adenomas and carcinomas may have been related to mercuric chloride exposure." Dr. Goodman commented on the statement in the genetic toxicology section that the induction of a high number of complex chromosomal aberrations implicated mercuric chloride as a major cause of damage, as opposed to cytotoxicity, which would be expected to produce mainly simple breaks. He considered this the sort of insight he would like to see more often, and asked that a reference or two be added.

Dr. Klaassen suggested that there be an expanded discussion of how the three forms of mercury — mercury vapor, organic mercury, and inorganic mercury salts — differ in toxicity. Dr. Boorman said a paragraph would be added. Dr. Carlson commented on the poor survival in dosed male rats and wondered about the adequacy of the study in male rats. Dr. J.K. Haseman, NIEHS, noted that survival to week 90 was about 60% in both dosed groups so a majority of animals survived long enough to be considered at risk for neoplasms. Further, since there was a positive effect for carcinogenicity, the low survival is less of a concern. Dr. Zeise thought the level of evidence in female rats should have been *some evidence* based on the two squamous cell papillomas in the high-dose group with supporting hyperplasia and similar increases in male rats. Dr. Boorman responded that based on only two neoplasms the staff did not think there was an unequivocal association with the chemical. Dr. McKnight argued that the three renal tubule neoplasms in high-dose male mice supported *some evidence*, particularly in view of zero incidence in concurrent controls and historical controls for water gavage studies. Dr. Boorman said the staff had considered this level; however, step sections of the kidneys failed to uncover any additional lesions in male or female mice, weakening the support for a chemical-associated effect.

Mr. Beliczky moved that the Technical Report on mercuric chloride be accepted with the revisions discussed, with the conclusions as written for male rats, *some evidence of carcinogenic activity*, for female rats and male mice, *equivocal evidence of carcinogenic activity*, and for female mice, *no evidence of*

carcinogenic activity, and with deletion of the second sentence: "An increased incidence of thyroid follicular cell adenomas and carcinomas may have been related to mercuric chloride exposure." The motion was tabled for lack of a second. Mr. Beliczky then moved that the conclusions be accepted as written including the second sentence. Dr. Garman seconded the motion. Dr. Goodman offered an amendment that the sentence have the word "marginally" added. Dr. Klaassen seconded the amendment, which was accepted by nine yes to one no votes (Dr. Zeise). Dr. Zeise offered an amendment that the conclusion for male mice be changed to *some evidence of carcinogenic activity*. Dr. McKnight seconded the amendment, which was defeated by eight no to two yes votes (Drs. McKnight, Zeise). Dr. Zeise offered an amendment that the conclusions for female rats be changed to *some evidence of carcinogenic activity*. The amendment was tabled for lack of a second. Mr. Beliczky's second motion to accept the conclusions as written with the second sentence amended to include the word "marginally" was then accepted by nine yes to one no votes (Dr. Zeise).